HEPATITIS C
April 2003

1: Am J Epidemiol 2003 Mar 1;157(5):467-71
Variability in the incidence of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infection among young injecting drug users in New YorkCity.
Des Jarlais DC, Diaz T, Perlis T, Vlahov D, Maslow C, Latka M, Rockwell R, Edwards V, Friedman SR, Monterroso E, Williams I, Garfein RS.
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Cohort studies of young (aged 18-30 years) injecting drug users recruited in 1997-1999 in the Harlem and Lower East Side areas of New York City, New York, were used to assess the incidence of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). The authors found that HIV incidence was low at both sites: 0.8/100 person-years at the Harlem site and 0/100 person-years at the Lower East Side site. In contrast, HBV incidence was moderate (12.2/100 person-years) at the Harlem site and high (30.7/100 person-years) at the Lower East Side site. Similarly, HCV incidence was moderate (9.3/100 person-years) at the Harlem site and high (34.0/100 person-years) at the Lower East Side site. Results show that high rates of HBV and HCV transmission do not imply high rates of HIV transmission, even within an area of high HIV seroprevalence.
PMID: 12615611 [PubMed - indexed for MEDLINE]

2: Clin Chem 2003 Mar;49(3):479-86
Low-positive anti-hepatitis C virus enzyme immunoassay results: an important predictor of low likelihood of hepatitis C infection.
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BACKGROUND: Tests for hepatitis C antibodies (anti-HCV enzyme immunoassays) are usually described as positive or negative. Several studies, mainly in blood donors, have found that specimens with low signal/cutoff (S/C) ratios are commonly negative when tested with a recombinant immunoblot assay (RIBA) or for HCV RNA.
METHODS: We retrospectively reviewed 17 418 consecutive anti-HCV results from a screening program for high-risk veterans; 2986 (17.1%) samples were anti-HCV-positive, and 490 (16.4%) had S/C ratios <or=3.7 (low positive).
Additional tests were performed in 1814 anti-HCV-positive individuals. RESULTS: RIBA was performed in 263 patients with low-positive anti-HCV; results were negative in 86%, indeterminate in 12%, and positive in 2%. Only 16 of 140 individuals (11%) with low-positive anti-HCV values were HCV RNA-positive, whereas HCV RNA was positive in 90% of 1435 individuals with high-positive anti-HCV values (P <0.0001). Compared with those with high-positive anti-HCV, individuals with low-positive anti-HCV values were older (P <0.0001) and were less likely to have risk

factors for HCV (P <0.0001 for most), multiple increased alanine aminotransferase (ALT) activity values (30% vs 81%; P <0.0001), or positive anti-hepatitis B core antigen (19% vs 59%; P <0.0002). Among 634 individuals with high anti-HCV titers and multiple increased ALT activity values, 95% were HCV RNA-positive. CONCLUSIONS: The S/C ratio is important even in high-risk individuals; laboratories should report the S/C ratio along with anti-HCV EIA results and perform supplemental RIBA testing in those with low-positive values to avoid reporting false-positive results.
PMID: 12600961 [PubMed - indexed for MEDLINE]

3: Clin Chem 2003 Mar;49(3):450-4
Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients.
Rossi E, Adams L, Prins A, Bulsara M, de Boer B, Garas G, MacQuillan G, Speers D, Jeffrey G.
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BACKGROUND: Determining the stage of fibrosis by liver biopsy is important in managing patients with hepatitis C virus infection. We investigated the predictive value of the proprietary FibroTest score to accurately identify significant fibrosis in Australian hepatitis C patients. METHODS: Serum obtained from 125 confirmed hepatitis C patients before antiviral therapy was analyzed for haptoglobin, alpha(2)-macroglobulin, apolipoprotein A1, bilirubin, and gamma-glutamyltransferase activity, and the FibroTest score was computed. Liver fibrosis pathology was staged according to a defined system on a scale of F0 to F4. We used predictive values and a ROC curve to assess the accuracy of FibroTest scores. RESULTS: The prevalence of significant fibrosis defined by liver biopsy was 0.38. The most useful single test for predicting significant fibrosis was serum alpha(2)-macroglobulin (cutoff value, 2.52 g/L; sensitivity, 75%; specificity, 67%). The negative predictive value of a FibroTest score <0.1 was 85%, and the positive predictive value of a score >0.6 was 78%. Although 33 of the 125 patients had FibroTest scores <0.1 and were therefore deemed unlikely to have fibrosis, 6 (18%) had significant fibrosis. Conversely, of the 24 patients with scores >0.6 who were likely to have significant fibrosis, 5 (21%) had mild fibrosis. Of the 125 patients in the cohort, 57 (46%) could have avoided liver biopsy, but discrepant results were recorded in 11 of those 57 (19%). CONCLUSION: The FibroTest score could not accurately predict the presence or absence of significant liver fibrosis.
Publication Types:
Validation Studies
PMID: 12600957 [PubMed - indexed for MEDLINE]

4: Gastroenterology 2003 Mar;124(3):642-50
Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study.
Samuel D, Bizollon T, Feray C, Roche B, Ahmed SN, Lemonnier C, Cohard M, Reynes M, Chevallier M, Ducerf C, Baulieux J, Geffner M, Albrecht JK, Bismuth H, Trepo C.
Centre HepatoBiliaire, Hopital Paul Brousse Assistance Publique-Hopitaux de Paris, Faculte de Medecine Paris Sud, EA 3541, EPI 99-41 et Association Claude Bernard, Villejuif, France. didier.samuel@pbr.ap-hop-paris.fr
BACKGROUND AND AIMS: Hepatitis C virus (HCV) reinfection after liver transplantation is frequent and leads to chronic hepatitis and cirrhosis. The use of antiviral therapy in this situation remains controversial. This study aimed to assess

the safety and efficacy of interferon alfa-2b plus ribavirin for recurrent hepatitis C following liver transplantation. METHODS: Transplant recipients with recurrent chronic hepatitis C were randomized to receive either no treatment or therapy with interferon alfa-2b (3 MU 3 times a week) plus 1000-1200 mg/day ribavirin for 1 year. Patients were followed up for 6 months after the end of treatment. The primary end point was loss of HCV RNA 6 months after the end of treatment. RESULTS: Fifty-two patients were randomized (treatment, 28; placebo, 24). Sixteen patients were withdrawn from the study; 12 (43%) were from the treated group (mainly for anemia [7 patients]) and 4 (17%) from the control group. In the treated group, serum HCV RNA was undetectable in 9 patients (32%) at the end of treatment and 6 (21.4%) at the end of the follow-up period, whereas no patient in the control group lost HCV RNA at any point (P = 0.036 at the end of follow-up). However, there was no significant histologic improvement. CONCLUSIONS: The combination of interferon alfa-2b plus ribavirin induced a sustained virologic response in 21% of transplant recipients with recurrent hepatitis C. However, 43% discontinued therapy due to adverse events (primarily severe anemia). Strategies to enable treatment with lower doses of ribavirin need to be explored.
Publication Types:
Clinical Trial
Multicenter Study
Randomized Controlled Trial
PMID: 12612903 [PubMed - indexed for MEDLINE]

5: Hepatology 2003 Mar;37(3):577-89
Novel CD4+ and CD8+ T-cell determinants within the NS3 protein in subjects with spontaneously resolved HCV infection.
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Spontaneous resolution of hepatitis C virus (HCV) infection is a relatively infrequent event, and these individuals provide a unique opportunity to characterize correlates of protective immunity as an important first step in the development of vaccine candidates. The aim of this study was to directly and comprehensively enumerate HCV-nonstructural protein 3 (NS3) specific CD4(+) and CD8(+) T cells ex vivo from HLA diverse individuals who had been successful in spontaneously resolving HCV infection. We measured interferon gamma (IFN-gamma) production with an ELISPOT assay using magnetic bead-separated CD4(+) or CD8(+) T cells in response to autologous DCs that had been pulsed with 15mer per peptides overlapping by 11 amino acids and spanning all of the NS3 protein (150 total peptides). All subjects with spontaneously recovered HCV infection demonstrated vigorous and multispecific CD4(+) T-cell responses to NS3 peptides, and 6 of 10 subjects demonstrated CD8(+) T-cell responses. More importantly, we identified novel, previously unpredicted antigenic regions, which in most cases elicited high frequencies within a given individual. In conclusion, subjects who have spontaneously eradicated HCV infection up to 35 years earlier demonstrate persistent CD4(+) and CD8(+) T-cell responses specific to NS3. By providing a comprehensive screening of all potential T-cell epitopes contained in the NS3 region, our strategy defines the breadth of the T-cell response and identifies novel, unpredicted specificities.
PMID: 12601356 [PubMed - indexed for MEDLINE]

6: Hepatology 2003 Mar;37(3):590-9
Influence of ethnicity in the outcome of hepatitis C virus infection and cellular immune response.
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This study was performed to examine the immunologic basis for the apparent ethnic difference in clinical outcome of hepatitis C virus (HCV) infection between African Americans (AA) and Caucasian Americans (CA). To this end, we recruited 99 chronically HCV-infected and 31 spontaneously HCV-cleared subjects for clinical, virologic, and immunologic analysis. In particular, CD4-proliferative T-cell response to genotype 1-derived HCV antigens (core,
NS3-NS5) was examined in 82 patients chronically infected with genotype 1 (54 AA, 28 CA) and in all HCV-cleared subjects (14 AA, 17 CA). HCV-specific Th1 response also was examined in 52 chronic and 13 recovered subjects. Our results showed that HCV clearance was associated with a vigorous HCV-specific Th1 response irrespective of ethnic origin. Although the HCV-specific CD4 T-cell response clearly was weaker during chronic infection, AA ethnicity in this setting was associated with a significantly greater CD4-proliferative T-cell response to HCV, particularly to the nonstructural antigens (22% AA vs. 0% CA, P=.007) as well as better clinical parameters of liver disease. Interestingly, most HCV-specific CD4 T-cell proliferative responses in AA patients were unaccompanied by concurrent interferon gamma (IFN-gamma) production, suggesting a dysregulated virus-specific, CD4 T-cell effector function during chronic HCV infection. In conclusion, our results suggest that host ethnicity does influence the clinical outcome and antiviral T-cell response during HCV infection. AA ethnicity is associated with a more robust antiviral CD4 T-cell response than CA ethnicity, although these T cells are limited in direct virus or disease control due to their dysfunctional nature.
PMID: 12601357 [PubMed - indexed for MEDLINE]

7: Hepatology 2003 Mar;37(3):600-9
Prediction of treatment outcome in patients with chronic hepatitis C: significance of baseline parameters and viral dynamics during therapy.
Berg T, Sarrazin C, Herrmann E, Hinrichsen H, Gerlach T, Zachoval R, Wiedenmann B, Hopf U, Zeuzem S. Medizinische Klinik mit Schwerpunkt Hepatologie und Gastroenterologie,
Universitatsklinikum Charite, Campus Virchow-Klinikum, Humboldt-Universitat, Berlin, Germany.
In patients with chronic hepatitis C virus (HCV) infection scheduled for a 48-week treatment period, premature discontinuation of treatment was previously recommended if HCV-RNA levels remained detectable at week 24 of therapy. Considering the number of side effects and treatment costs, measurement of initial viral decline during therapy may identify virologic nonresponse earlier than 24 weeks. We retrospectively analyzed 260 European patients treated with standard or pegylated interferon alfa (IFN-alpha) and ribavirin for 24 to 48 weeks. Early prediction of virologic response by HCV-RNA decline at weeks 4 and 12 (Versant Quantitative [branched DNA (bDNA) 3.0]; Bayer Diagnostics, Emeryville, CA; and Qualitative [transcription-mediated amplification (TMA)] HCV RNA assay; Bayer Diagnostics) as well as clinical, biochemical, virologic, and histologic baseline parameters were analyzed by logistic regression and receiver operating characteristic (ROC) curves. A viral load at treatment week 4 above 450,000 IU/mL and at week 12 above 30,000 IU/mL was 100% predictive for virologic nonresponse in all patients. From multivariate logistic regression analysis of all patients, independent predictors for sustained virologic response were: genotypes 2 and 3 (P <.0001), a low baseline gamma-glutamyltransferase (GGT) level (P <.0001), a high baseline alanine aminotransferase level (P =.002), and a low baseline viral load (P =.04). None of the latter 3 factors were predictive for sustained virologic response when analysis was restricted to the subgroup of genotypes 2- and 3-infected patients. In

conclusion, virologic nonresponse can be predicted early at week 12 of treatment independent from the applied therapeutic regimen based on a cutoff level for HCV RNA of 30,000 IU/mL. This algorithm recognizes 53.7% of nonresponders previously identified at week 24 of treatment.
PMID: 12601358 [PubMed - indexed for MEDLINE]

8: Hepatology 2003 Mar;37(3):610-21
Interferon alfa regulated gene expression in patients initiating interferon treatment for chronic hepatitis C.
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Interferon alfa (IFN-alpha) is an approved therapeutic agent for chronic hepatitis C. To directly characterize the effects of IFN-alpha in humans, we used microarrays to profile gene expression in peripheral blood mononuclear cells (PBMCs) from hepatitis C patients treated with IFN-alpha. Seven patients were studied using two strategies: (1) in vivo: PBMCs were collected immediately before the first dose of IFN-alpha, and 3 and 6 hours after the dose; (2) ex vivo: PBMCs that were collected before the first IFN-alpha dose were incubated with IFN-alpha for 3 and 6 hours. The microarray datasets were analyzed with significance analysis of microarrays (SAM) to identify genes regulated by IFN-alpha. We identified 516 named genes up-regulated at least 2-fold, at a false discovery rate (FDR) of less than 1%. In vivo and ex vivo studies generated similar results. No genes were identified as regulated differently between these 2 experimental conditions. The up-regulated genes belonged to a broad range of functional pathways and included multiple genes thought to be involved in the direct antiviral effect of IFN-alpha. Of particular interest, 88 genes directly relating to functions of immune cells were up-regulated, including genes involved in antigen processing and presentation, T-cell activation, lymphocyte trafficking, and effector functions, suggesting that IFN-alpha up-regulates multiple genes involving different aspects of immune responses to enhance immunity against hepatitis C virus. In conclusion, IFN-alpha-inducible genes can be identified in human PBMCs in vivo as well as ex vivo. Signature changes associated with different treatment outcomes may be found among these genes.
PMID: 12601359 [PubMed - indexed for MEDLINE]

9: Hepatology 2003 Mar;37(3):568-76
Ribavirin and interferon is effective for hepatitis C virus clearance in hepatitis B and C dually infected patients.
Liu CJ, Chen PJ, Lai MY, Kao JH, Jeng YM, Chen DS.
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Ribavirin and interferon (IFN) are an effective treatment in 30% to 60% of patients with chronic hepatitis C. Whether they are also effective in dually infected patients with hepatitis B and C is unknown. Twenty-four patients with chronic hepatitis seropositive for both hepatitis B surface antigen and antibody to HCV received ribavirin 1,200 mg daily for 6 months, together with 6 million units (MU) IFN-alpha 2a thrice weekly for 12 weeks and then 3 MU for another 12 weeks. Serum HCV RNA was positive in 21 patients (group I, serum HBV DNA positive in 17 patients) and negative in 3 patients (group II, all HBV DNA positive) by Amplicor (Cobas Amplicor Monitor, Roche Diagnostics, Branchburg, NJ). Serum alanine aminotransferase (ALT), HCV RNA, and hepatitis B virus (HBV) DNA were monitored regularly for 12 months. Another 30 patients with chronic hepatitis C alone receiving the same regimen, served as controls. The serum HCV clearance rate in group I patients (43%) was comparable with that in controls (60%, P =.63) 24 weeks posttreatment. The serum ALT normalization rate in group I and group II patients was 43% and 0%,

respectively, 24 weeks posttreatment. After treatment, resurgence of HBV and HCV was encountered in 4 group I patients and 1 group II patient, respectively. In conclusion, in hepatitis B and C dually infected patients, combination of IFN with ribavirin can achieve a sustained HCV clearance rate comparable with hepatitis C alone. In dually infected patients, the treatment may alter the dominant, ruling hepatitis virus.
PMID: 12601355 [PubMed - indexed for MEDLINE]

10: Hepatology 2003 Mar;37(3):520-7
Comment in:
Hepatology. 2003 Mar;37(3):507-9.
Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis.
Velazquez RF, Rodriguez M, Navascues CA, Linares A, Perez R, Sotorrios NG, Martinez I, Rodrigo L.
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Department of Gastroenterology, Hospital de Cabuenes, Gijon, Spain.
Better knowledge of the risk factors associated with the appearance of hepatocellular carcinoma (HCC) could improve the efficacy of surveillance programs. A total of 463 patients aged 40 to 65 years with liver cirrhosis in Child-Pugh class A or B were included in a program of early diagnosis. The predictive value of different risk factors was evaluated using the Kaplan-Meier method and Cox regression model. Thirty-eight patients developed HCC. In the multivariate analysis, 4 variables showed an independent predictive value for the development of HCC: age 55 years or older, antibody to hepatitis C virus (anti-HCV) positivity, prothrombin activity 75% or less, and platelet count less than 75 x 10(3)/mm(3). According to the contribution of each of these factors to the final model, a score ranging between 0 and 4.71 points was constructed to allow the division of patients into 2 different risk groups. The low-risk group included those with a score of 2.33 points or less (n = 270; 4 with HCC; cumulative incidence of HCC at 4 years, 2.3%), and the high-risk group included those with a score greater than 2.33 (n = 193; 34 with HCC; cumulative incidence of HCC at 4 years, 30.1%) (P =.0001). In conclusion, a simple score made up of 4 clinical and biological variables allowed us to distinguish 2 groups of cirrhotic patients at high and low risk for the development of HCC. We believe this score can be useful in establishing a subset of cirrhotic patients in whom a surveillance program for early detection of HCC could be unjustified.
PMID: 12601348 [PubMed - indexed for MEDLINE]

11: Hepatology 2003 Mar;37(3):493-503
Genetic polymorphisms and the progression of liver fibrosis: a critical appraisal.
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Liver fibrosis is a highly dynamic process in which multiple genes interact with environmental factors. Recent human epidemiologic studies have identified possible polymorphisms in a number of candidate genes that influence the progression of liver fibrosis. These genetic factors could explain the broad spectrum of responses to the same etiologic agent found in patients with chronic liver diseases. Polymorphisms in genes encoding immunoregulatory proteins, proinflammatory cytokines, and fibrogenic factors may influence disease progression in patients with alcohol-induced liver disease, primary biliary cirrhosis, or chronic hepatitis C. However, some of the studies have yielded contradictory results. For example, conflicting results have been obtained in studies assessing the role of mutations in the hemochromatosis gene on fibrosis progression in patients with chronic hepatitis C. Large-scale, well-designed

studies are required to clarify the actual role of this factor and other genetic variants in liver fibrosis.
Publication Types:
Review
Review, Tutorial
PMID: 12601343 [PubMed - indexed for MEDLINE]

12: J Gen Virol 2003 Mar;84(Pt 3):545-54
Characterization of secreted and intracellular forms of a truncated hepatitis C virus E2 protein expressed by a recombinant herpes simplex virus.
Lucas M, Tsitoura E, Montoya M, Laliotou B, Aslanoglou E, Kouvatsis V, Entwisle C, Miller J, Klenerman P, Hadziyannis A, Hadziyannis S, Borrow P, Mavromara P.
Molecular Virology Laboratory, Hellenic Pasteur Institute, 127 Vas. Sofias Ave, Athens 115 21, Greece.
A replication-defective herpes simplex virus type 1 (HSV-1) recombinant lacking the glycoprotein H (gH)-encoding gene and expressing a truncated form of the hepatitis C (HCV) E2 glycoprotein (E2-661) was constructed and characterized. We show here that cells infected with the HSV/HCV recombinant virus efficiently express the HCV E2-661 protein. Most importantly, cellular and secreted E2-661 protein were both readily detected by the E2-conformational mAb H53 and despite the high expression levels, only limited amounts of misfolded aggregates were detected in either the cellular or secreted fractions. Furthermore, cell-associated and secreted E2-661 protein bound to the major extracellular loop (MEL) of CD81 in a concentration-dependent manner and both were highly reactive with sera from HCV-infected patients. Finally, BALB/c mice immunized intraperitoneally with the recombinant HSV/HCV virus induced high levels of anti-E2 antibodies. Analysis of the induced immunoglobulin G (IgG) isotypes showed high levels of IgG2a while the levels of the IgG1 isotype were significantly lower, suggesting a Th1-type of response. We conclude that the HSV-1 recombinant virus represents a promising tool for production of non-aggregated, immunologically active forms of the E2-661 protein and might have potential applications in vaccine development.
PMID: 12604804 [PubMed - indexed for MEDLINE]

13: J Pediatr Hematol Oncol 2003 Mar;25(3):184-92
Comment in:
J Pediatr Hematol Oncol. 2003 Mar;25(3):183.
Hepatitis B and C infection in children undergoing chemotherapy or bone marrow transplantation.
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Despite preventive measures, patients who have cancer or who undergo bone marrow
transplantation remain at higher risk of viral infection since they often receive multiple blood products. This category of patients also includes subjects from countries that are highly endemic for hepatitis B virus and hepatitis C virus infection and who travel to developed countries for specialized treatment. This review discusses the current opinions concerning the diagnostic, clinical, and therapeutic aspects of hepatitis B and C virus infection in different groups of patients: children with chronic infection before chemotherapy, children infected during chemotherapy or bone marrow transplantation, and patients with chronic infection after the end of treatment.
Publication Types:
Review
Review, Tutorial
PMID: 12621235 [PubMed - indexed for MEDLINE]

14: Mol Carcinog 2003 Mar;36(3):130-41
Hepatocyte growth factor, transforming growth factor alpha, and their receptors as combined markers of prognosis in hepatocellular carcinoma.
Daveau M, Scotte M, Francois A, Coulouarn C, Ros G, Tallet Y, Hiron M, Hellot MF, Salier JP.
INSERM Unite 519 and Institut Federatif de Recherches Multidisciplinaires surles Peptides, Faculte de Medecine-Pharmacie, Rouen France.
A change in the balance between proliferation and apoptosis in the course of hepatocellular carcinoma (HCC) development and progression has been suspected. We wanted to identify related genes whose mRNA levels could provide markers of severity and prognosis after resection. The extent of cell apoptosis, proliferation, and differentiation was measured with a terminal deoxynucleotidyl transferase-mediated deoxyuridine 5-triphosphate-biotin nick-end labeling assay, and the Ki-67 index was determined in paired tumor and cirrhotic tissue samples from patients who had undergone HCC resection after diagnosis of hepatitis C-related or alcoholism-related cirrhosis. These patients included two groups with highly versus poorly differentiated tumor cells, and the latter was split into two subgroups of those with versus without early recurrence. The mRNA levels for various apoptosis-related or proliferation-related genes and those for the growth factor/receptor systems were measured by quantitative reverse transcriptase-polymerase chain reaction in paired tumor and cirrhotic liver samples from every patient, and some of the corresponding proteins were detected by immunohistochemistry. In all instances, protein expression was highly heterogeneous within groups and similar between groups. In contrast, some differences in mRNA level between tumor and cirrhotic tissues were quite informative. Low levels of hepatocyte growth factor and transforming growth factor alpha mRNAs were found concomitantly in highly differentiated tumors, whereas over expression of mRNAs for the cognate receptors c-met and epidermal growth factor receptor were found in poorly differentiated tumors and primarily in patients with early tumor recurrence. These results argue for growth factor-dependent HCC development and provide novel and combined prognosis markers after HCC surgery.

PMID: 12619035 [PubMed - indexed for MEDLINE]